

# The Spectrum of the Antiphospholipid Syndrome: A Matter of Perspective



For many years, rheumatologists diagnosed what is now known as antiphospholipid syndrome (APS) as systemic lupus erythematosus (SLE). We knew that many of these patients would never manifest other features of SLE but rather demonstrate only thrombosis, thrombocytopenia, or pregnancy loss. As a matter of fact, one or more of those manifestations was likely the reason the patient came to our attention in the first place.

Owing to the work of individuals such as Harris, Hughes, Gharavi, and Alarcon-Segovia<sup>1-5</sup>, we have come to appreciate that these patients do not have lupus but rather a separate but related entity, the APS. Although many of us have become complacent with this classification<sup>6</sup>, we may still be unclear in many circumstances which patients to treat, when to treat, and how to treat.

APS is first and foremost a clinical disorder. At least one specific laboratory abnormality must be present to classify a patient as APS: either anticardiolipin antibody (IgG or IgM) and/or a lupus anticoagulant (LAC). However, a positive laboratory test is insufficient for the diagnosis. Indeed, there is no rationale in even testing for their presence in the absence of the clinical features<sup>7-11</sup>. When these laboratory markers are determined in a clinically inappropriate situation, the physician is left in a potential quandary: should this asymptomatic patient be treated or is it safe to ignore these laboratory abnormalities?

Although the first question is why the test was ordered in the first place, the more important question is whether the presence of an antiphospholipid antibody (aPL) or LAC is a risk factor for one or more clinical manifestations. The answer to this question directly determines whether treatment is indicated.

The approach to the management of patients with aPL is very much dependent upon the perspective of the attending physician. Although practitioners in other specialties may

attend to patients with APS, hematologists, obstetricians, and rheumatologists are most often involved in their management. Faced with a patient with APS or one with merely positive blood work, the management decisions will likely vary among these specialties.

To the hematologist, APS means dealing with hypercoagulability. The patient has a history of venous and/or arterial thrombosis and the goal of therapy is to prevent further thromboembolic events utilizing anticoagulant therapy. APS patients may be adequately treated with low intensity warfarin in the case of venous thrombotic disease or may require high intensity anticoagulation when there is a history of arterial thrombosis<sup>12,13</sup>. In either case, the hematologist sees a patient at risk for recurrent thrombotic events when confronted with APS.

Patients with APS present to the obstetrician with recurrent pregnancy losses (RPL), either early or late, preeclampsia or HELLP syndrome (hemolysis, elevated liver function test, low platelet count), intrauterine growth restriction in the fetus, or placental abruption. Unlike other patients with APS, there may be no history of thromboembolic events. Therapy in these cases is more controversial. Several therapeutic modalities have been investigated and currently heparin in combination with aspirin is the more common treatment option<sup>14,15</sup>, although this regimen has recently been challenged<sup>16</sup>.

Perhaps the more complex cases with APS present to the rheumatologist. These patients typically have more than one manifestation, including thrombosis, RPL, thrombocytopenia, nephritis, Raynaud's phenomenon, rash such as livedo reticularis, or a vasculitic eruption. Positive antinuclear antibodies may be found suggesting a diagnosis of SLE. Depending upon the clinical picture, one or more different treatment modalities may be used including anticoagulants, aspirin, prednisone, hydroxychloroquine, or intravenous gammaglobulin. In general, the rheumatologist will encounter the patient with multi-

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*See A study of 75 pregnancies in patients with APS, page 2025*

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ple manifestations more often than either of the above two specialties.

This differential experience of physicians with patients with APS influences the management of all patients classified as APS, regardless of the manifestations. To best illustrate this point, let us examine the problem of recurrent pregnancy loss.

At the 9th International Symposium on Antiphospholipid Antibodies in September 2000, Branch commented on his previous belief that standardized treatment protocols for pregnancy in women with aPL would be available by the end of the 1990s<sup>17</sup>. Indeed, many also thought that the clinical and laboratory criteria for APS had been satisfactorily defined at the 1999 Sapporo Conference<sup>6</sup>. Meanwhile, however, classification criteria and therapeutic protocols have again become controversial after publication of a number of studies highlighting not only the broad spectrum of patients involved — including the paper by Huang, *et al* in this issue<sup>18</sup> — but also the questionable benefit of any therapeutic intervention at all<sup>16</sup>.

There have been numerous studies over the last 15 years evaluating the efficacy of acetylsalicylic acid<sup>16</sup>, prednisone<sup>19</sup>, unfractionated<sup>15</sup> and low molecular weight heparin<sup>20</sup>, and most recently intravenous gammaglobulin<sup>21</sup>, alone or in various combinations. While many of the studies have been well designed and appropriately powered and analyzed, the varied outcomes are frequently not reproducible at other centers.

In our opinion, based on treating women with APS in our clinic for the past 15 years, the discrepancy in experience with respect to the therapeutic efficacy in the treatment of RPL is likely due to patient heterogeneity, laboratory variability, and the disparate perspectives of the obstetrician, hematologist and rheumatologist.

The example of a 30-year-old woman with a history of 3 pregnancy losses all between 8 and 10 weeks' gestation who has an IgM anticardiolipin antibody of 25 MPL illustrates our point. Current guidelines from the American College of Obstetrics and Gynecology (ACOG) and others<sup>22,23</sup> state that this patient requires treatment with heparin and aspirin. The guidelines do not recommend that further investigations be undertaken, but rather that the positive serology combined with this clinical picture is sufficient to justify intervention. Some obstetricians might recommend further investigation. For example, what if further investigation revealed the presence of a uterine septum? What abnormality would be deemed the more clinically significant? If ACOG guidelines were followed to the letter, the septum would never have been detected, as no anatomic investigations would have been pursued. Our experience in evaluating many patients with first trimester losses has revealed numerous patients with this exact clinical picture.

A hematologist seeing this patient with a history of recurrent miscarriage and aPL would likely follow other guidelines recently published by Ginsberg, *et al*<sup>24</sup>, which also recommend treatment for pregnant women with aPL without further

investigation. Of course the hematologist would be more concerned that this woman would be at risk for a thromboembolic event, further justifying anticoagulant therapy. Does the fact that this woman has no history of thromboembolism change her risk of a thrombotic event during a future pregnancy? Should this patient be viewed in the same light as a woman with one pregnancy loss at 24 weeks characterized by intrauterine growth restriction and placental infarction, with a history of venous thromboembolism? Depending upon the attending physician's orientation, we submit that in all probability, these two patients may be viewed as having the identical disease with the same risks during a pregnancy.

The question prompted by these two case scenarios relates to treatment. If it is accepted that heparin and aspirin is the appropriate therapy for the treatment of recurrent pregnancy loss in women with an aPL, then both patients should be so treated. However, we believe these patients to be quite different, but representative of the spectrum of APS. One randomized controlled trial has been published that found 85% of women with RPL and an aPL had a successful pregnancy outcome whether treated with aspirin alone or placebo<sup>16</sup>. Our own experience with patients fulfilling the same criteria resulted in a 51% successful outcome<sup>19</sup> without treatment, whereas Rai, *et al* had only a 10% success rate in untreated cases<sup>25</sup>. These 3 studies, with success rates in untreated patients ranging from 10 to 85%, highlight the lack of agreement regarding this population. Perhaps the variation from center to center reproducing results of similar therapeutic modalities is related to the large variation in baseline success rates in the untreated patient population. This variation, in turn, may simply be due to the possibility we are all investigating slightly different subgroups within the spectrum of APS.

Women with RPL and an aPL must be viewed as a diverse population rather than as a single disease entity with equivalent risk requiring identical therapy. We must all appreciate that APS describes a wide spectrum, perhaps requiring formal subclassification<sup>26</sup>, and patients must be evaluated and treated individually. Further, treatment must be directed towards clinical disease and not laboratory markers, particularly in light of the continuing controversy regarding the significance of IgM aCL and lower titers of IgG aCL<sup>26</sup>. It is our belief that further controlled clinical trials addressing the problem of recurrent pregnancy loss in women with aPL will serve to emphasize the clinical heterogeneity in this group of patients and support a more rational approach to therapy.

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